A BIOMIMETIC APPROACH TO BENZOPHENANTHRIDINE ALKALOID FROM PROTOBERBERINE ALKALOID

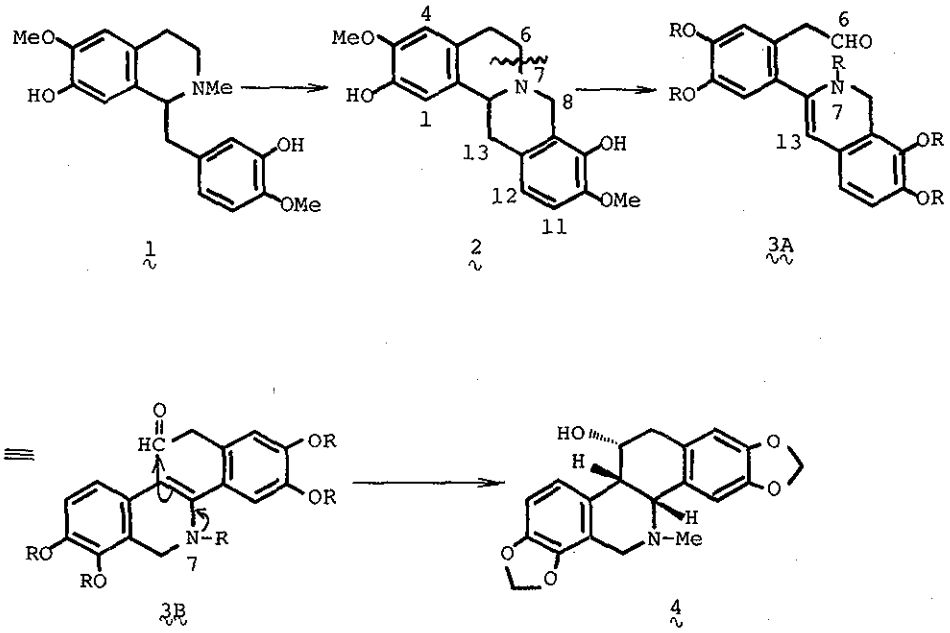
Tetsuji Kametani,* Makoto Takemura, Masataka Ihara, Keiichiro Fukumoto,
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan
and Keiichi Takahashi
The Sendai Institute of Heterocyclic Chemistry,
Kawauchi-Sanjuninmachi, Sendai 980, Japan

10-Hydroxy-2,3,11-trimethoxyberbine (5) is transformed along by a biogenetic pattern into 7,8-dihydro-10-hydroxy-2,3,11-trimethoxybenzophenanthridine (11) via the methine base (6).

The benzophenanthridine alkaloids (4) are biosynthesised through cleavage of the C_6-C_7 bond of berbines (2), which are formed in plants from reticuline (1) type benzylisoquinolines, followed by joining of C_6 to C_{13} in 3 as shown in a biosynthesis of (+)-chelidonine (4).[1]

Along this scheme Onda has synthesised benzophenanthridine alkaloids chelerythrine and sanguinarine by a photolytic electrocyclic reaction from the methine bases derived from protoberberines.[2] A similar type of reaction is applied in the synthesis of chelerythrine analog.[3] We have also investigated a synthesis of benzophenanthridine alkaloids followed by a biogenetic line in connection with our previous work[4] and here wish to report a novel formation of the benzophenanthridine (11) from the methine base (6) by a phenol oxidation.[4]

Scheme 1



1 2 3A

≡

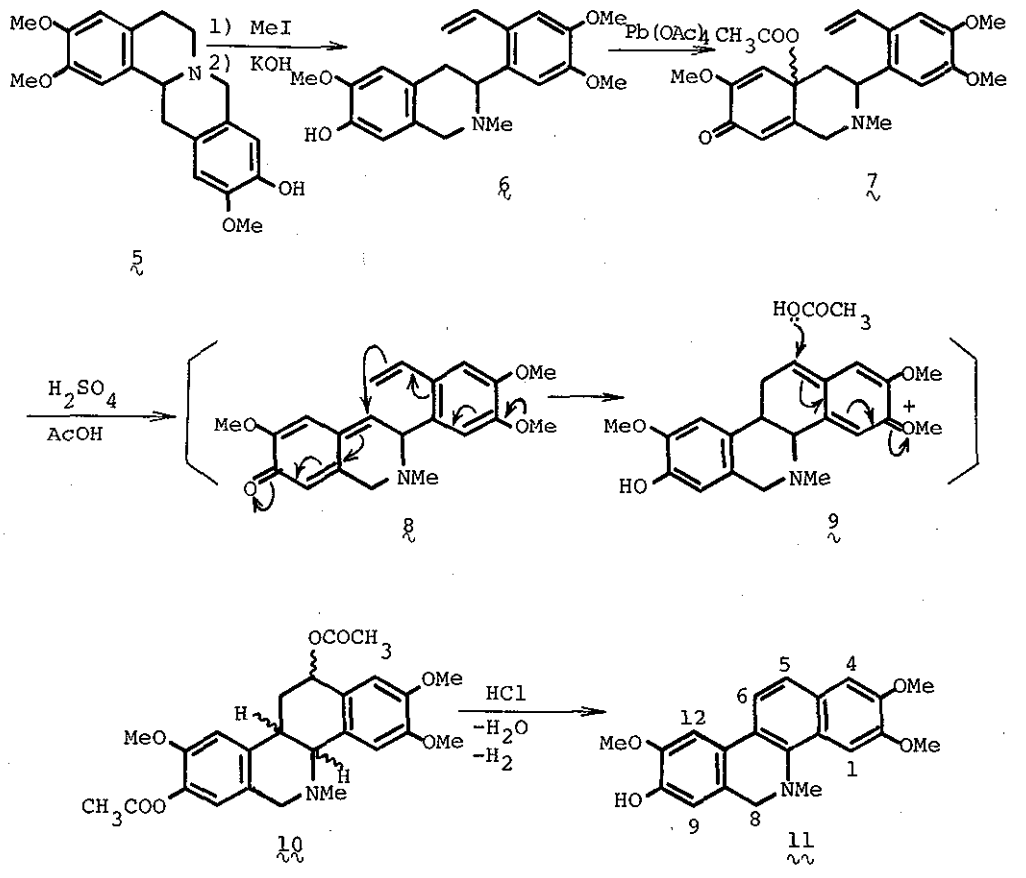
3B 4

10-Hydroxy-2,3,11-trimethoxyberbine (5)[5] methiodide, was subjected to Hofmann degradation with potassium hydroxide in methanol as usual[6] to give the methine base (6) in a moderate yield,† m.p. 155 ∿ 156°C [$\delta(CDCl_3)$ 2.16 (3H, s, NMe), 5.15 (1H, dd, J 2 and 11 Hz, $CH=CH_2$) and 5.50 (1H, dd, J 2 and 17 Hz, $CH=CH_2$]. This was oxidised with lead tetraacetate[7] in acetic acid at room temperature for 0.5 hr to afford the p-quinol acetate (7)† [ν_{max} ($CHCl_3$) 1743 ($OCOCH_3$) and 1680, 1658 and 1630 cm^{-1} (dienone)], which without purification was treated with sulphuric acid in acetic anhydride at 0°, then at room temperature to furnish the benzophenanthridine derivative (10)† [ν_{max} ($CHCl_3$) 1760 and 1730 cm^{-1}]. Treatment of this product with hydrochloric acid in boiling ethanol gave 7,8-dihydro-10-hydroxy-2,3,11-trimethoxy-benzophenanthridine (11)† , m.p. 220° by a spontaneous dehydration and dehydrogenation of the initial product. This product showed a typical uv absorption [λ_{max} (EtOH) 312, 278, and 220 nm] of the benzophenanthridine system[8] and a phenolic hydroxyl group at 3550 cm^{-1}. This structure was supported by the nmr spectrum revealing N-methyl at 2.60, three O-methyls at 3.97 (2 x OMe) and 4.06, methylene protons at 4.12 (s) and two vicinal aromatic protons at 7.47 and 7.70 as each doublet having J 8.0 Hz, in addition to four isolated aromatic protons at 6.84, 7.10, 7.27 and 7.67.

The formation mechanism is explained as follows. Intermediacy of the quinone methides (8) derived from the p-quinol acetate (7) would be responsible for the formation of benzophenanthridine (10) through 9 as shown in Scheme 2.

The methine bases having no hydroxyl group at C_7-position on the isoquinoline system are not transformed into the benzophenanthridine

Scheme 2


MeO
MeO
1) MeI
2) KOH
N
OH
OMe
HO
NMe
OMe
Pb(OAc)4
CH3COO
O
5
6
7
H2SO4
AcOH
8
9
HOCOCH3
+
10
OCOCH3
H
HCl
-H2O
-H2
CH3COO
11
12
1
4
5
6
8
9

type of compounds by a treatment of lead tetraacetate or palladium chloride[9].

This novel reaction seems to have general method for a synthesis of benzophenanthridine[10] and we are now investigating a scope and application of our finding.

REFERENCES AND NOTES

† The yields in all reactions were not been optimised but moderate.

1 A. R. Battersby, R. J. Francis, E. A. Ruveda, and J. Staunton, Chem. Comm., 1965, 89; A. R. Battersby, R. J. Francis, M. Hirst, R. Southgate, and J. Staunton, Chem. Comm., 1967, 602; A. R. Battersby, J. Staunton, H. R. Wiltshire, R. J. Francis, and R. Southgate, J. C. S. Perkin I, 1975, 1147.

2 M. Onda, K. Yonezawa, and K. Abe, Chem. and Pharm. Bull. (Japan), 1969, 17, 404; 1971, 19, 31. cf. M. Onda and K. Kawakami, Chem. and Pharm. Bull. (Japan), 1972, 20, 1484; M. Onda, K. Yuasa, J. Okada, A. Kataoka, and K. Abe, Chem. and Pharm. Bull. (Japan), 1973, 21, 1333.

3 V. Šmula, R. H. F. Manske, and R. Rodrigo, Canad. J. Chem., 1972, 50, 1544.

4 T. Kametani, K. Fukumoto, and F. Satoh, Bioorg. Chem., 1974, 3, 430; T. Kametani and K. Fukumoto, Synthesis, 1972, 657; T. Kametani, K. Fukumoto, and M. Ihara, Bioorg. Chem.,in press.

5 T. Kametani, K. Nyu, S. Ikeda, T. Tominaga, and R. Iwashiro, J. Pharm. Soc. Japan, 1973, 93, 1116.

6 T. Kametani, M. Takemura, K. Takahashi, M. Takeshita, M. Ihara, and K. Fukumoto, J. Chem. Soc. Perkin I, 1975, 1012; T. Kametani, M. Takemura, K. Fukumoto, T. Terui, and A. Kozuka, J. Chem. Soc. Perkin I, 1974, 2678 and refs. cited herein.

7 B. Umezawa and O. Hoshino, Heterocycles, 1975, 3, 1005.

8 M. Shamma, "The Isoquinoline Alkaloids, Chemistry and Pharmacology," Academic Press, New York, 1972, p. 341 ∿ 342.

9 O. L. Chapman, M. R. Engel, J. P. Springer, and J. C. Clardy, J. Amer. Chem. Soc., 1971, 93, 6696; O. L. Chapman and C. L. McIntosh,

Chem. Comm., 1971, 383.

10 I. Ninomiya, Heterocycles, 1974, 2, 105.

Received, 21st October, 1976